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Case Number: T 0015/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 30 April 2009

Appellant: (Opponent)
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Respondent: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 30 October 2006 rejecting the opposition filed against European patent No. 1117401 pursuant to Article 102(2) EPC 1973.

Composition of the Board:

Chairman: U. Oswald
Members: A. Lindner
T. Karamanli

Summary of Facts and Submissions

I. European patent No. 1 117 401 based on application No. 99 956 504.7 was granted on the basis of a set of 24 claims.

The independent claims read as follows:

"1. A topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt. % and a pharmaceutical acceptable vehicle therefor.

12. Use of moxifloxacin or a pharmaceutically useful hydrate or salt thereof for the preparation of a topical composition comprising 0.1 to 1.0 wt. % of moxifloxacin for treating or preventing ophthalmic infections."

II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a) EPC 1973 for lack of inventive step and under Article 100(c) 1973 EPC for amendments that contain subject-matter extending beyond the content of the application as originally filed.

III. In a letter dated 11 July 2006, the opponent argued that the subject-matter of claims 1 to 11 was not in accordance with the requirements of Article 54(5) EPC 1973.

IV. The documents cited during the opposition and appeal proceedings included the following:

(1) US-A-5 607 942

(3) WO 90/01933

(10) Survey of ophthalmology, 50 (Sup. 1), 2005, S32-S45

(12) Arch. Ophthalmology, 123, 2005, 1282-1283

(13) Ophthalmology, 112(11), 2005, 1992-1996

(14) Ophthalmology, 113(6), 2006, 955-959

(15) Survey of ophthalmology, 50 (Sup. 1), 2005, S55-S63

(16) Ophthalmic fluoroquinolones market share

(17) Package insert of Vigamox

(18) Antimicrobial agents and chemotherapy, 41(1), 1997, 101-106

(19) WHO Drug Information, vol. 11, no. 4, 1997, 265-266 and 279

(20) Current Medical Research and Opinion, vol. 24, no. 12, 2008, 3479-3486

V. In the decision pronounced on 14 September 2006, the opposition division rejected the opposition. Its principal findings in the reasons for the decision posted on 30 October 2006 were as follows: in connection with the grounds for opposition according to Article 100(c) EPC 1973, it was held that formula (I) contained an obvious error, as the substituent A was omitted. As a consequence, it appeared that moxifloxacin was not encompassed by formula (I). However, when considering the original application in its entirety, it was clear that moxifloxacin should be included in formula (I), so that compositions comprising moxifloxacin at a concentration of 0.1 to 1.0 wt% were meant to be part of the content of the original application. Moreover, the correction of

formula (I) on page 3 of patent under appeal was found to be allowable under Rule 88 EPC 1973. In addition, the subject-matter of claims 1 to 11 was not open to objection under Article 54(5) EPC 1973. As regards inventive step, the opposition division defined document (3), which disclosed ophthalmic compositions comprising a fluoroquinolone antibiotic such as ciprofloxacin, as the closest prior art. Starting from the teaching of this document, the person skilled in the art, trying to enhance the antibiotic efficacy, would not choose moxifloxacin as the antibiotic agent. As a consequence, the requirements of Article 56 EPC 1973 were met.

VI. The opponent (appellant) lodged an appeal against that decision.

VII. With his letter dated 14 September 2007, the respondent (patentee) submitted document (19).

VIII. With his letter dated 30 March 2009, the respondent submitted document (20).

IX. Oral proceedings took place on 30 April 2009.

X. The appellant's arguments can be summarised as follows:

As regards the grounds for opposition raised under Article 100(c) EPC 1973, it was pointed out that the original application disclosed neither the correct structure of moxifloxacin nor the fact that moxifloxacin was encompassed by formula (I). The cross-reference in the original application to document (1) was ambiguous and could therefore not be used for

interpreting formula (I). In addition, the original application, which referred to compositions for otic, nasal and ophthalmic application, did not disclose compositions for exclusively ophthalmic use. As a consequence, there was no disclosure in the original application of a topical ophthalmic pharmaceutical composition comprising moxifloxacin in a concentration of 0.1 to 1.0 wt.% and an acceptable pharmaceutical vehicle.

Regarding inventive step, document (3) was defined as the closest prior art. It was obvious to replace the fluoroquinolone derivates of document (3) by moxifloxacin in order to obtain more efficient antibacterial compositions for topical ophthalmic use in the light of document (18), which disclosed a higher antibacterial activity of moxifloxacin as compared with ciprofloxacin against key ophthalmic pathogens. It was emphasised that a shift of the problem from enhanced efficacy to enhanced penetration was not allowable.

XI. The respondent's arguments can be summarised as follows:

In connection with the grounds for opposition raised under Article 100(c) EPC 1973, it was reasoned that the original application contained obvious errors. However, the skilled person knew the structure of moxifloxacin and recognised in the light of the disclosure in its entirety that moxifloxacin was encompassed by formula (I). Moreover, there was a basis for compositions for ophthalmic use in the original application, as the ophthalmic application was the preferred embodiment.

As regards inventive step, document (3) was defined as the closest prior art. The substitution of moxifloxacin as active agent in the topical ophthalmic antimicrobial compositions for other fluoroquinolones such as ciprofloxacin or ofloxacin resulted in enhanced antimicrobial efficacy, which was achieved by improved penetration of the active agent into the ocular tissue. The combination of documents (3) and (18) did not render obvious an enhanced antimicrobial activity in connection with topical ophthalmic compositions, as document (18) was silent about penetration. However, penetration, like antimicrobial activity, was an indispensable prerequisite for antimicrobial efficacy. Moreover, document (18) did not even show enhanced antimicrobial activity against Pseudomonas aeruginosa, which was the most important key opthalmic pathogen.

XII. The appellant requested that the decision under appeal be set aside and that the European patent be revoked.

The respondent requested that the appeal be dismissed (main request) or in the alternative, that the decision under appeal be set aside and the European patent be maintained in amended form on the basis of the auxiliary request filed at the oral proceedings of 30 April 2009.

Reasons for the Decision

1. The appeal is admissible.

2. Admissibility of documents (18) and (19):

Document (18), submitted by the appellant with the letter dated 11 July 2006, was filed at a late stage of the opposition procedure. In the decision under appeal, the opposition division did not decide on its admissibility. Document (19) was filed with the respondent's reply to the appeal.

The board sees no reason not to admit these documents into the appeal proceedings. These documents contain additional evidence relevant to the decision and the parties did not raise any objections as to their admissibility.

3. Main request:

3.1. Claim 1 - Article 100(c) EPC 1973:

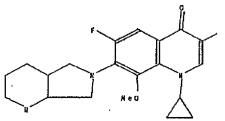
As can be seen from point I above, claim 1 as granted relates to a topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt.% and a pharmaceutical acceptable vehicle therefor.

In contrast, claim 1 as originally filed concerns a topical ophthalmic, otic or nasal pharmaceutical composition comprising an antimicrobial effective amount of one or more compounds of formula (I).

3.1.1. Structural composition of moxifloxacin:

The basis for moxifloxacin can be found on page 5, lines 21-30, of the original application, which reads:

"The compound Moxifloxacin is most preferred. Moxifloxacin has the following structure:

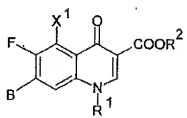


"

This passage is contradictory, as moxifloxacin carries a carboxyl group in position 3 (see document (19)) rather than a methyl group as shown in the formula above. Moreover, the diaza-bicyclic structure is not restricted to the stereospecific isomer. Theoretically, there are two possible explanations for this contradiction: either the formula is wrong or it was intended to deliberately define a new structure for the term moxifloxacin, in which case the formula would be correct and moxifloxacin would have a new meaning. The second alternative can, however, be excluded: the person skilled in the art knows that "moxifloxacin" exists as an official International Nonproprietary Name (INN) (see document (19)). Therefore, he would not use this existing INN name for a different chemical structure. As a consequence, it is clear that the formula intended to depict moxifloxacin contains an obvious error and that moxifloxacin, having a carboxylic group in position 3 and the stereospecific form as defined in the INN list, was meant.

3.1.2. Inclusion of moxifloxacin in formula (I):

It therefore remains to be established whether moxifloxacin having the structure as defined in the INN list is encompassed by formula (I). Reference is made to claim 6 of the original application, where it is clearly indicated that the compound of formula (I) comprises moxifloxacin. However, at first sight the chemical structure of formula (I) (see page 4 and claim 1 of the original application) does not have a methoxy group in position 8 of the quinolone ring system and thus does not appear to include moxifloxacin. But a closer look reveals that formula (I) does not comprise substituent A, which according to the definition given in the text (see page 4, line 17) should be present and which inter alia includes C-OCH_3. Formula (I) is therefore erroneous. It is defined as follows:



wherein:

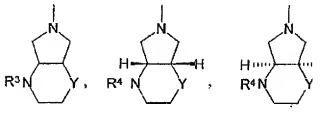
A is CH, CF, CCl, C-OCH_3, or N

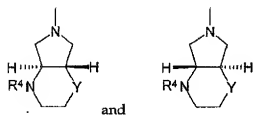
X^1 is halogen, NH_2, or CH_3

R^1 is C_1 to C_3 alkyl, FCH_2CH_2, cyclopropyl or phenyl, optionally mono-, di- or tri-substituted by halogen, or A and R^1 can form a bridge of formula C-O-CH_2-$CH(CH_3)$;

R^2 is H, C_1 to C_3 alkyl (optionally substituted by OH, halogen or NH_2), 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl; and

B is a selected from the group consisting of :





and

wherein :

Y is O or CH_2;

R^3 is C_2-C_5 alkoxyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C-CO_2R', CH=CH-CO_2R'or CH_2CH_2-CN,

wherein:

R' is or C_1 to C_3 alkyl;

R^4 is H, C_1 to C_3 alkyl, C_2-C_5 alkoxyl,CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C-CO_2R', CH=CH-CO_2R', CH_2CH_2-CN or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

wherein :

R' is H or C_1 to C_3 alkyl; and their pharmaceutically useful hydrates and salts.

A priori, there are four alternatives for removing the contradiction between the formula and the text:

(a) the structure of formula (I) is correct and the definition for substituent A was erroneously inserted into the text and has to be ignored;

(b) substituent A is in position 2 of the quinolone ring system;

(c) substituent A is in position 8 of the quinolone ring system;

(d) substituent A is in both positions 2 and 8 of the quinolone ring system.

Taking into consideration the disclosure in the original application in its entirety, alternatives (a) and (b) are to be excluded, as they do not encompass moxifloxacin. Alternatives (c) and (d), however, yield technically reasonable solutions, which also include the correct stereospecific form for the residue B. From the content of the original application, it cannot be determined whether alternative (c) or (d) constitutes the correct initially intended version. A correction of formula (I) according to Rule 88 EPC 1973 would therefore not be possible. However, in view of the existence of alternatives (c) and (d), the board concludes that the disclosure in the original application in its entirety contains a basis for moxifloxacin being encompassed by formula (I), even if the correct version of the formula cannot be defined.

The respondent additionally argued that the original application (see page 4, lines 33-35) contained a

cross-reference to United States Patent No. 5,607,942 (document (1)), which allowed a correct interpretation of formula (I) in the sense that substituent A was in position 8 (alternative (c)). The board does not agree in view of the fact that this cross-reference is not clear and unambiguous. The passage cited above states that "further details regarding structure, preparation, and physical properties of Moxifloxacin and other compounds of formula (I) are provided in United States Patent No. 5,607,942". A closer look at document (1) reveals that it comprises neither any physical properties of nor a specific method for preparing moxifloxacin. As a consequence, the content of document (1) cannot be taken into consideration for the interpretation of formula (I) of the present application.

3.1.3. Introduction of 0.1 to 1.0 wt.% of moxifloxacin:

The basis can be found on page 7, lines 10-13, of the original application, where this feature is disclosed in connection with the compounds of formula (I). In view of the fact that moxifloxacin constitutes a compound according to formula (I) (see point 3.1.2 above), the range of 0.1 to 1.0 wt.% is originally disclosed for moxifloxacin.

3.1.4. Introduction of the feature "pharmaceutically useful hydrate or salt thereof":

The basis for this feature can be found on page 5, line 20, of the original application, again in connection with the compounds of formula (I). As moxifloxacin constitutes a compound according to

formula (I) (see point 3.1.2 above), this feature is originally disclosed in connection with moxifloxacin.

3.1.5. Restriction of claim 1 to ophthalmic compositions:

The original application relates to topical ophthalmic, otic or nasal pharmaceutical compositions. The deletion of the otic and nasal compositions and the selection of the ophthalmic compositions does not introduce new subject-matter, particularly, as the original application envisages purely ophthalmic compositions (see page 2, lines 3-6).

3.2. Claim 12 - Article 100(c) EPC 1973:

The reasoning of point 3.1 applies *mutatis mutandis* to independent claim 12.

3.3. As a consequence, none of the amendments introduces subject-matter that extends beyond the content of the original application, so that the ground for opposition according to Article 100(c) EPC 1973 does not prejudice the maintenance of the patent as granted.

3.4. Inventive step - Articles 100(a) and 56 EPC 1973:

The present invention concerns the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic bacterial infections. The compositions should be particularly effective against key ophthalmic pathogens (see page 2, lines 5-6 and 25-27, of the patent under appeal).

Document (3) constitutes the closest prior art. It relates to topical antibiotic pharmaceutical compositions for the treatment of ophthalmic bacterial infections and inflammations (see page 1, lines 1-4 and 9-19), comprising the fluoroquinolone derivatives ciprofloxacin, norfloxacin, ofloxacin, difloxacin and pefloxacin as antibacterial agents (see page 1, lines 19-22, and claim 1).

3.4.1. Claim 1:

It is well-known in the art that there is a constant need for improved compositions and methods of treatment based on the use of antibiotics (see also page 2, lines 25-28, of the contested patent) that are more effective than existing antibiotics and less prone to the development of resistance. In ophthalmology, this applies in particular to key ophthalmic pathogens. Accordingly, the technical problem with regard to the disclosure of document (3) is to be defined as follows: provision of a topical composition for treating or preventing ophthalmic infections which is more effective against key ophthalmic pathogens. The problem was solved by a composition as defined in claim 1, i.e. by a topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt.%.

The contested patent itself does not contain any evidence of improved efficacy or to restricted development of resistance. However, additional evidence in the form of post-published documents comprising comparative tests was submitted during first-instance

proceedings, which shows enhanced penetration of moxifloxacin into the ocular tissue as compared with ciprofloxacin or ofloxacin (see e.g. document (10), abstract). In view of the fact that, of the five active agents specifically disclosed in document (3), ciprofloxacin is structurally closest to moxifloxacin, the comparison with ciprofloxacin is considered to be representative of all the active agents in document (3).

As regards the relationship between penetration and efficacy, it is noted that the antibacterial efficacy of a topically administered drug is the combination of its antibacterial activity against given pathogens, which is commonly expressed by the MIC value, and its ability to penetrate tissue in order to gain access to the part of the body where it is needed. As it was already known that moxifloxacin has antibacterial activity, the demonstration of enhanced penetration has to be interpreted as proof of enhanced efficacy. As a consequence, the problem has been plausibly solved.

When assessing whether it is obvious for the skilled person to replace the active agents of document (3) by moxifloxacin in order to obtain a more effective antibacterial ophthalmic composition, it is necessary to take into account the teaching of document (18), which comprises the MIC50 and MIC90 values for BAY 12-8039 (= moxifloxacin) and other antimicrobial agents such as ciprofloxacin against various pathogens including the key ophthalmic pathogens MSSA (=Staphylcoccus aureus/methicillin sensitive), MRSA (Staphylcoccus aureus/methicillin resistant), Staphylococcus epidermis and Pseudomonas aeruginosa.

Table 1 (see the MIC90 values) shows that moxifloxacin is about eight times more potent against MSSA, about 60 times as potent against MRSA, about four times more potent against Staphylococcus epidermis than ciprofloxacin and about half as potent as ciprofloxacin against Pseudomonas aeruginosa. Document (18) is silent about penetration. However, the skilled person, trying to provide a more effective ophthalmic composition, would as a first step identify those active agents which are more active against key ophthalmic pathogens than the fluoroquinolones used in document (3). Without a significant antibacterial potency, there can be no reasonable efficacy, no matter how good the penetration into the ocular tissue may be. In the light of the data according to table 1 in document (18), the skilled person would select moxifloxacin, as it is much more potent against the key ophthalmic pathogens MSSA, MRSA and Staphylococcus epidermis. The fact that he will later discover enhanced penetration in the ocular tissue as compared to ciprofloxacin can only be regarded as a bonus effect, which in itself cannot establish an inventive step. It is additionally noted that the concentration range of 0.1 to 1.0% is a normal concentration, which does not give rise to any non-obvious effects that might constitute an inventive step. This fact was not contested by the respondent. As a consequence, the subject-matter of claim 1 does not meet the requirements of Article 56 EPC 1973.

3.4.2. Additional arguments of the respondent:

Moxifloxacin was less potent than ciprofloxacin against Pseudomonas aeruginosa, which was the most dangerous pathogen in eye infections where it played a role in

about 20% of all cases. As ophthalmologists did not in general identify the pathogens but treated them empirically, a topical ophthalmological composition had to be effective against all the relevant ocular pathogens and certainly against Pseudomonas aeruginosa.

This argumentation is not in line with the problem as defined in the original application (see page 2, lines 3-6), which states that there is "a need for improved compositions and methods of treatment... that are more effective than existing antibiotics **against key ophthalmic pathogens...**" [emphasis by the board]. This passage does not specify that the improved compositions and methods of treatment need to be more effective against the key ophthalmic pathogens, let alone against all the relevant key ophthalmic pathogens. The ophthalmologist does in general treat empirically, but there are situations where he may want to specifically treat infections caused by MSSA or MRSA rather than by Pseudomonas aeruginosa, and in these cases, which are encompassed by the subject-matter of claim 1 and are included in the technical problem as defined in the original application, the enhanced efficacy of compositions comprising moxifloxacin was obvious in the light of the above reasoning. As a consequence, this argument cannot succeed.

3.4.3. Claim 12:

In view of the fact that the use of topical compositions comprising 0.1 to 1.0 wt.% of moxifloxacin for treating or preventing ophthalmic infections was found obvious, the subject-matter of claim 12, which is formulated as a Swiss-type claim, lacks an inventive

step for the same reasons as outlined in connection with claim 1. As a consequence, the requirements of Article 56 EPC 1973 are not met.

3.4.4. In view of the above, the ground for opposition under Article 100(a) EPC 1973 prejudices the maintenance of the patent as granted.

4. Auxiliary request:

4.1. Admissibility:

The filing of the auxiliary request was a reaction of the respondent to the discussion at the oral proceedings about the limiting character of the feature "topical ophthalmic pharmaceutical composition". Moreover, the only modification compared with the main request consisted in the deletion of the product claims, so that the appellant was not taken by surprise. The board therefore admitted the auxiliary request into the appeal proceedings exercising its discretion under Article 13(1) RPBA.

4.2. In view of the fact that claim 1 of the auxiliary request is identical to claim 12 of the main request, the reasoning set out above in paragraph 3.4.3 with regard to claim 12 of the main request also applies to claim 1 of the auxiliary request. The requirements of Article 56 EPC 1973 are therefore not met.

4.3. As a consequence, taking into consideration the amendments made by the respondent, the patent and the invention to which it relates, do not meet the requirements of the EPC.

5. Since none of the respondent's requests is allowable, the patent is to be revoked (Article 101(2) and (3)(b) EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The European patent is revoked.

The Registrar: The Chairman:

N. Maslin U. Oswald